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1-Butyl-3-methylimidazolium Bromide as a Solvent and Precatalyst for Stetter Reaction

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Stetter reaction between aromatic aldehydes and acrylonitrile/ethyl acrylate performing in [Bmim]Br in the presence of NaOH is described. *N*-Heterocyclic carbene (NHC) generates *in situ* is shown to be an efficient catalyst. Benzoin condensation also occured as side reaction.

Keywords: [Bmim]Br, *N*-Heterocyclic carbene, catalyst, Stetter reaction.

INTRODUCTION

Stetter reaction is the cross-coupling reaction between aldehydes and Michael acceptors. The reaction is generally catalysed by *N*-heterocyclic carbenes (NHCs) generated *in situ* by deprotonation of azolium salts [1], *i.e*. thiazolium, triazolium and imidazolium salts (Fig. 1).

Stetter reaction proceeds through addition of NHC **2**, generated *in situ* from deprotonation of corresponding azolium ion **1**, to aldehyde **3** follows by a proton transfer process of adduct **4** to form Breslow intermediate **5**. Subsequent conjugate addition of **5** to the Michael acceptor **6** leads to the conjugate adduct **7**, which undergoes another proton transfer process. Liberation of NHC **2** from the resulting intermediate **8** provides 1,4-dicarbonyl adduct **9** [2] (**Scheme-I**).

N-heterocyclic carbene catalyzed-Stetter reaction is a simple synthetic method for affording 1,4-dicarbonyl compounds, which are important intermediates in synthesis of various natural and medicinal compounds, such as *cis*-jusmon and dihydrojusmon, (±)-*trans*-sabinene hydrate and haloperidol [3-5] (**Schemes II-IV**).

Upon treatment with base, 1-butyl-3-methylimidazolium bromide ([Bmim]Br), commonly used as reaction medium, has been reported to provide an effective NHC catalyst for benzoin condensation [6]. In continuation of our studies on performing Stetter reaction in ionic liquids [7,8] herein, we wish to report

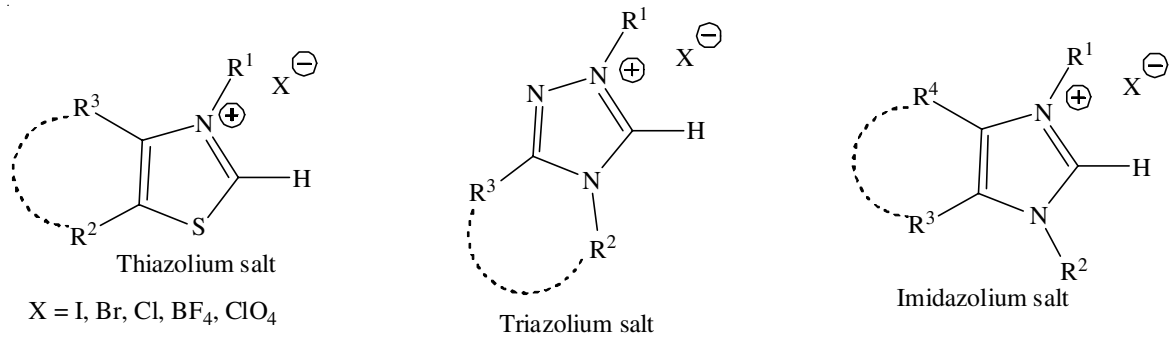
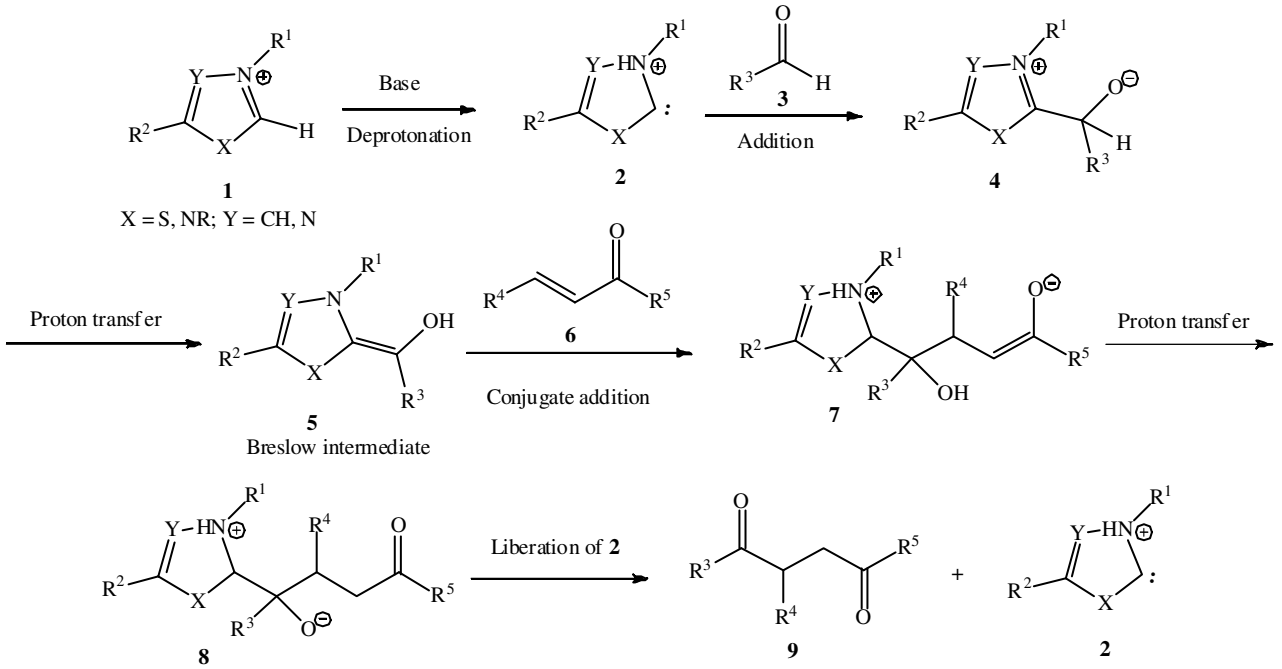
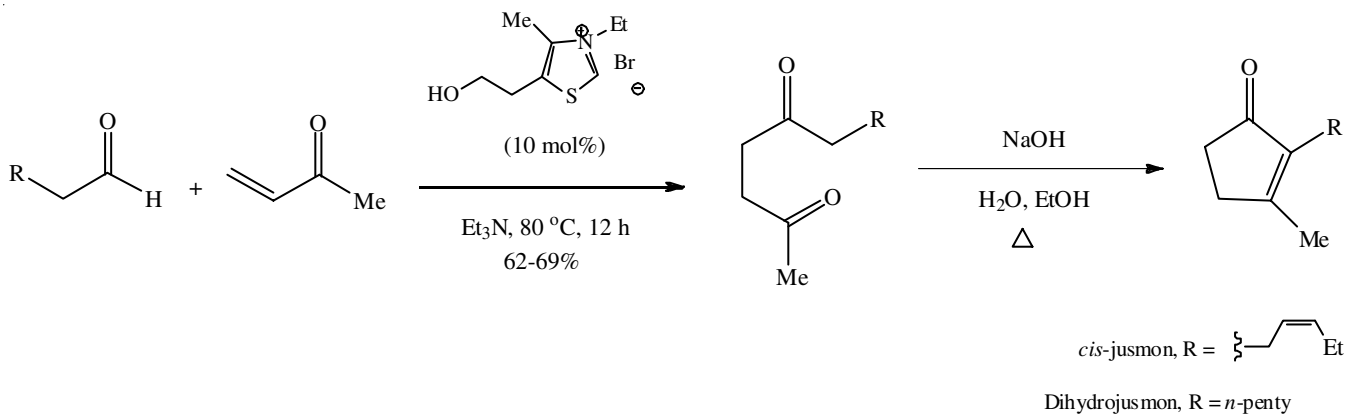


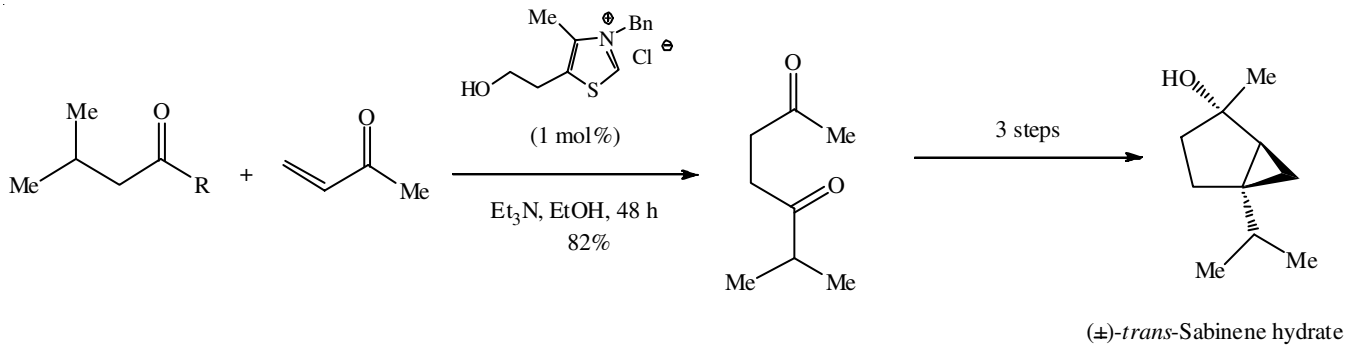
Fig. 1. Azolium salts generally utilized as precatalyst for Stetter reaction



Scheme-I: The reaction pathway for Stetter reaction catalysed by NHCs catalyst



Scheme-II: Synthesis of *cis*-jusmon and dihydrojusmon

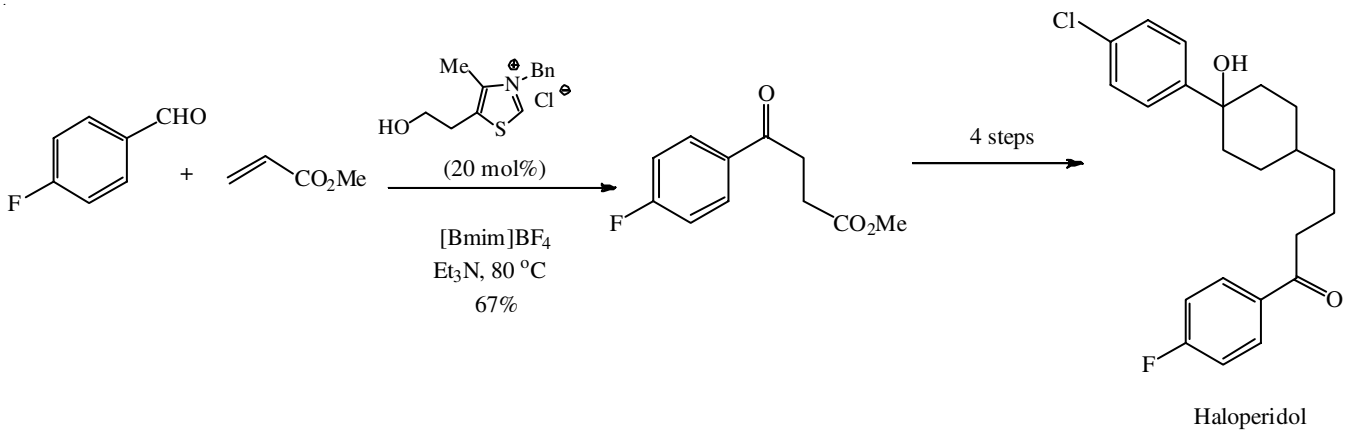


Scheme-III: Synthesis of (±)-*trans*-sabinene hydrate

a successful employment of [Bmim]Br as a solvent and NHC precursor in Stetter reaction.

EXPERIMENTAL

All chemicals in the experiment were commercially available and used directly without further purification. Melting points were determined in capillary tubes in a Buchi B 545 apparatus. The products were identified by comparison of their melting points and spectral data (IR, ^{1}H & ^{13}C NMR) with those in the authentic samples. FT-IR spectra were obtained as KBr disks on a Shimadzu spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded using a Varian Mercury plus (400 MHz FT-NMR).



Scheme-IV: Synthesis of haloperidol

General procedure for the Stetter reaction between aromatic aldehydes (10a-d) and acrylonitrile (11)/ethyl acrylate (15): To a grinding mixture of [Bmim]Br (**12**) (0.219 g, 1 mmol) and NaOH (0.008 g, 0.2 mmol) was added corresponding aromatic aldehyde **10** (1.0 mmol) and acrylonitrile (**11**)/ethyl acrylate (**15**) (2 mmol) and the mixture was heated at 80 ºC for 8-13 h. After completion of the reaction (monitored by TLC, eluant hexane/dichloromethane, 1:1), the mixture was cooled to room temperature and extracted with dichloromethane (3 × 30 mL). The organic phase was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by preparative thin layer chromatography (silica gel, elution with dichloromethane).

4-Phenyl-4-oxobutanenitrile (13a): White crystals; m.p.: 74-76 ºC (lit. 74-76 ºC) [9]; IR (KBr, ν_{max}, cm^{-1}): 3069, 2955, 2257, 1692, 1596, 1450, 1332, and 1218; ^{1}H NMR δ: 7.97 (2H, d, *J* = 7.8 Hz, 2′- and 6′-*H*), 7.63 (1H, t, *J* = 7.8 Hz, 4′-*H*), 7.51 (2H, t, *J* = 7.8 Hz, 3′- and 5′-*H*), 3.40 (2H, t, *J* = 7.2 Hz, CH_2CH_2CN), 2.79 (2H, t, *J* = 7.2 Hz, CH_2CH_2CN); ^{13}C NMR δ: 11.9, 34.4, 119.4, 128.1, 128.9, 133.9, 135.7, 195.5.

4-(4′-Chlorophenyl)-4-oxobutanenitrile (13b): White crystals; m.p.: 72-73 ºC (lit. 72-73 ºC) [10]; IR (KBr, ν_{max}, cm^{-1}): 3136, 2951, 2257, 1676, 1562, 1466, 1327 and 1259; ^{1}H NMR δ: 7.88 (2H, d, *J* = 8.8 Hz, 2′- and 6′-*H*), 7.48 (2H, d, *J* = 8.8 Hz, 3′- and 5′-*H*), 3.34 (2H, t, *J* = 7.2 Hz, CH_2CH_2CN) and 2.78 (2H, t, *J* = 7.2 Hz, CH_2CH_2CN); ^{13}C NMR δ: 11.8, 34.2, 119.1, 129.3, 129.4, 133.9, 140.6, 194.2.

4-(4′-Tolyl)-4-oxobutanenitrile (13c): White crystals; m.p.: 75-77 ºC (lit. 75-77 ºC) [9]; IR (KBr, ν_{max}, cm^{-1}): 3065, 2920, 2252, 1689, 1399, 1331, 1225, 1184 and 1006; ^{1}H NMR δ: 7.85 (2H, d, *J* = 8.4 Hz, 2′- and 6′-*H*), 7.28 (2H, d, *J* = 8.4 Hz, 3′- and 5′-*H*), 3.38 (2H, t, *J* = 7.2 Hz, CH_2CH_2CN), 2.78 (2H, t, *J* = 7.2 Hz, CH_2CH_2CN), 2.43 (3H, s, Ar-CH_3); ^{13}C NMR δ: 11.9, 29.8, 34.2, 119.1, 128.1, 129.5, 133.3, 144.9, 201.2.

4-(Pyridin-4-yl)-4-oxobutanenitrile (13d): Yellow crystals; m.p.: 135-137 ºC; IR (KBr, ν_{max}, cm^{-1}): 3069, 2955, 2923, 2257, 2681, 1692, 1580, 1450, 1332, 1218 and 1002; ^{1}H NMR δ: 8.75 (2H, d, *J* = 8.4 Hz, 2′- and 6′-*H*), 7.88 (2H, d, *J* = 8.4 Hz, 3′- and 5′-*H*), 3.00 (2H, t, *J* = 7.2 Hz, CH_2CH_2CN), 2.75 (2H, t, *J* = 7.2 Hz, CH_2CH_2CN); ^{13}C NMR δ: 14.9, 38.8, 119.3, 122.6, 135.0, 135.3, 150.4, 198.8.

Benzoin (14a): White crystals; m.p.: 134-136 ºC (lit. 134-136 ºC) [11]; IR (KBr, ν_{max}, cm^{-1}): 3418, 2935, 1678, 1597, 1450, 1341, 1207 and 757; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.92 (2H, d, *J* = 7.6 Hz, 2- and 6-*H*), 7.53 (1H, t, *J* = 7.6 Hz, 4-*H*), 7.39 (2H, t, *J* = 7.6 Hz, 3- and 5-*H*), 7.25–7.32 (5H, m, Ar*H*), 5.96 (1H, s, C*H*), 4.53 (1H, br s, O*H*); ^{13}C NMR ($CDCl_3$) δ: 76.1, 127.7, 128.6, 128.7, 129.2, 133.6, 133.9, 139.1, 198.8.

4,4′-Dichlorobenzoin (14b): White crystals; m.p.: 87-88 ºC (lit. 87-88 °C) [10]; IR (KBr, ν_{max}, cm^{-1}): 3423, 3070, 2928, 1674, 1590, 1487, 1401, 1251, 1091, 977 and 812; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.76 (2H, d, *J* = 8.8 Hz, 2- and 6-*H*), 7.33 (2H, d, *J* = 8.8 Hz, 3- and 5-*H*), 7.23 (2H, d, *J* = 8.4 Hz, 3- and 5′-*H*), 7.17 (2H, d, *J* = 8.4 Hz, 2′- and 6′-*H*), 5.82 (1H, s, C*H*); ^{13}C NMR ($CDCl_3$) δ: 75.6, 129.0, 129.2, 129.5, 130.5, 131.5, 134.8, 137.2, 140.7, 197.5.

4,4′-Dimethylbenzoin (14c): White crystals; m.p.: 75-76 ºC (lit. 75 ºC) [12]; IR (KBr, ν_{max}, cm^{-1}): 3410, 3059, 2931, 1679, 1594, 1447, 1263, 1092 and 753; ^{1}H NMR δ: 7.82 (2H, d, *J* = 8.8 Hz, 2- and 6-*H*), 7.22 (2H, d, *J* = 8.8 Hz, 3- and 5-*H*), 7.17 (2H, d, *J* = 8.4 Hz, 2′-*H* and 6′-*H*), 7.12 (2H, d, *J* = 8.4 Hz, 3′- and 5′-*H*), 5.89 (1H, s, C*H*), 2.34 (3H, s, Ar-CH_3), 2.29 (3H, s, Ar-CH_3); ^{13}C NMR ($CDCl_3$) δ: 21.2, 21.7, 75.9, 127.7, 129.3, 129.5, 129.8, 131.0, 136.4, 138.4, 144.9, 198.4.

4,4′-Pyridoin (14d): Yellow crystals; m.p.: 154-156 ºC; IR (KBr, ν_{max}, cm^{-1}): 3463, 3075, 2981, 2843, 1667, 1597, 1513, 1465, 1314, 1266, 1169, 1075, 828; ^{1}H NMR δ: 8.76 (2H, d, *J* = 8.4 Hz, 2- and 6-*H*), 8.56 (2H, d, *J* = 8.4 Hz, 3- and 5-*H*), 7.93 (2H, d, *J* = 8.8 Hz, 2′-*H* and 6′-*H*), 7.19 (2H, d, *J* = 8.8 Hz, 3′- and 5′-*H*), 6.09 (1H, s, C*H*); ^{13}C NMR ($CDCl_3$) δ: 75.6, 122.1, 122.6, 135.0, 137.4, 145.1, 150.4, 197.9.

Ethyl 4-phenyl-4-oxobutanoate (16a): Yellow liquid; IR (neat, ν_{max}, cm^{-1}): 3032, 2955, 1724, 1640, 1569, 1446, 1392, 1260, 1183; ^{1}H NMR δ: 7.98 (2H, d, *J* = 7.6 Hz, 2′- and 6′-*H*), 7.56 (1H, t, *J* = 7.6 Hz, 4′-*H*), 7.46 (2H, t, *J* = 7.6 Hz, 3′- and 5′-*H*), 4.16 (2H, q, *J* = 7.6 Hz, OCH_2CH_3), 3.31 (2H, t, *J* = 6.8 Hz, $CH_2CH_2CO_2CH_2CH_3$), 2.74 (2H, t, *J* = 6.8 Hz, $CH_2CH_2CO_2CH_2CH_3$), 1.26 (3H, t, *J* = 7.6 Hz, CO_2CH_2-CH_3); ^{13}C NMR δ: 14.2, 28.4, 33.5, 60.6, 128.1, 128.6, 133.3, 136.7, 172.9, 198.2.

Ethyl 4-(4′-dichlorophenyl)-4-oxobutanoate (16b): White crystals; m.p.: 55-57 ºC (lit. 56-58 ºC) [9]; IR (KBr, ν_{max}, cm^{-1}):

3004, 2955, 1745, 1689, 1599, 1443, 1330 and 1273; ^{1}H NMR δ: 7.86 (2H, d, *J* = 8.4 Hz, 2′- and 6′-*H*), 7.37 (2H, d, *J* = 8.4 Hz, 3′- and 5′-H), 4.08 (2H, q, *J* = 7.6 Hz, $CO_2CH_2CH_3$), 3.21 (2H, t, *J* = 6.8 Hz, $CH_2CH_2CO_2CH_2CH_3$), 2.68 (2H, t, *J* = 6.8 Hz, $CH_2CH_2CO_2CH_2CH_3$), 1.21 (3H, t, *J* = 7.6 Hz, $CO_2CH_2CH_3$); ^{13}C NMR δ: 14.2, 28.2, 33.3, 60.7, 128.9, 129.4, 134.9, 139.6, 172.7, 197.0.

Ethyl 4-(4′-tolyl)-4-oxobutanoate (16c): White crystals; m.p.: 64-65 ºC; IR (KBr, ν_{max}, cm^{-1}): 3066, 2956, 1741, 1691, 1596, 1451, 1323, 1175, 1005, 748; ^{1}H NMR δ: 7.86 (2H, d, *J* = 8.8 Hz, 2′- and 6′-*H*), 7.38 (2H, d, *J* = 8.8 Hz, 3′- and 5′-*H*), 4.08 (2H, q, *J* = 7.6 Hz, $CO_2CH_2CH_3$), 3.20 (2H, t, *J* = 6.8 Hz, $CH_2CH_2CO_2CH_2CH_3$), 2.68 (2H, t, *J* = 6.8 Hz, $CH_2CH_2CO_2CH_2CH_3$), 2.11 (3H , s, CH_3Ar), 1.22 (3H, t, *J* = 7.6 Hz, $CO_2CH_2CH_3$); ^{13}C NMR δ: 14.3, 28.4, 30.9, 33.1, 60.7, 128.9, 129.5, 134.9, 139.7, 172.8, 196.8.

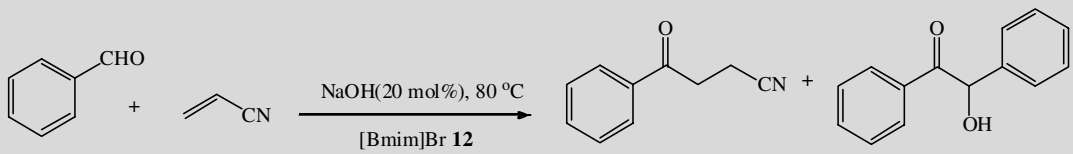
Ethyl 4-(pyridin-4-yl)-4-oxobutanoate (16d): Yellow liquid; IR (neat, ν_{max}, cm^{-1}): 3086, 2993, 2909, 1734, 1680, 1590, 1450, 1361, 1222, 1165, 1037; ^{1}H NMR δ: 8.75 (2H, d, *J* = 8.4 Hz, 2′- and 6′-*H*), 7.88 (2H, d, *J* = 8.4 Hz, 3′- and 5′-*H*), 4.12 (2H, q, *J* = 7.6 Hz, $CO_2CH_2CH_3$), 3.00 (2H, t, *J* = 6.8 Hz, $CH_2CH_2CO_2CH_2CH_3$), 2.71 (2H, t, *J* = 6.8 Hz, $CH_2CH_2CO_2CH_2CH_3$), 1.15 (3H, t, *J* = 7.6 Hz, $CO_2CH_2CH_3$); ^{13}C NMR δ: 14.1, 27.7, 33.4, 60.7, 122.8, 135.0, 150.4, 173.0, 196.8.

RESULTS AND DISCUSSION

In this study, we conducted Stetter reaction using [Bmim]Br as a solvent and precatalyst was conducted under reaction conditions similar to those reported by Grée *et al*. [5]. We began to briefly examine an effective amount of [Bmim]Br required for the nucleophilic coupling of benzaldehyde (**10a**) with acrylonitrile (**11**) in the presence of 20 mol% of NaOH at 80 ºC. Employment of 100 mol% of [Bmim]Br (**12**) was revealed to be optimal, satisfactorily affording the 1,4-addition product **13a** in 72% yield; benzoin (**14a**) resulted from benzoin condensation was obtained in 19% yield (Table-1, entry 3).

Under optimized condition, Stetter reaction between aromatic aldehydes **10b-d** and acrylonitrile (**11**) went on well to produce good yields of corresponding 1,4-addition products **13b-d** (Table-2, entries 1-3). Corresponding aroins **14b-d** also occurred as minor side products. Treatment of aromatic aldehyde **10a-d** with ethyl acrylate (**15**) similarly afforded corresponding 1,4-addition products **16a-d** as well as corresponding aroins **14a-d** as major and minor products, respectively (Table-2, entries 4-7). Lower yields (*ca*. 10%) of 1,4-addition products **16a-d** comparing with those of 1,4-adducts **13a-d** indicates that ethyl acrylate (**15**) is less reactive than acrylonitrile (**11**) towards Stetter reaction which in turn results in providing slightly increasing yields (3-11%) of aroins from benzoin condensation.

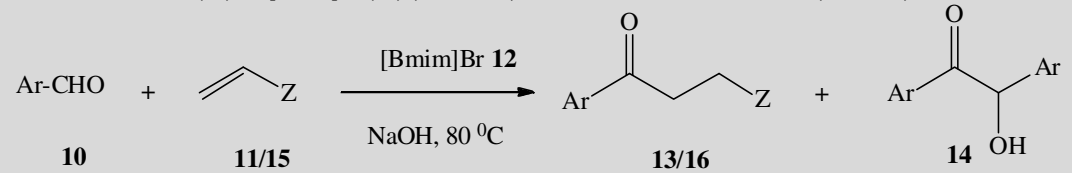
TABLE-1
BRIEF EXAMINATION OF EFFECTIVE AMOUNT OF [Bmim]Br (**12**) REQUIRED FOR STETTER REACTION BETWEEN BENZALDEHYDE (**10a**) AND ACRYLONITRILE (**11**) AT 80 °C



10a **11** **13a** **14a**

Entry	Mol% **12**	Yield **13a** (%)	Yield **14a** (%)
1	20	39	13
2	50	70	19
3	100	72	19

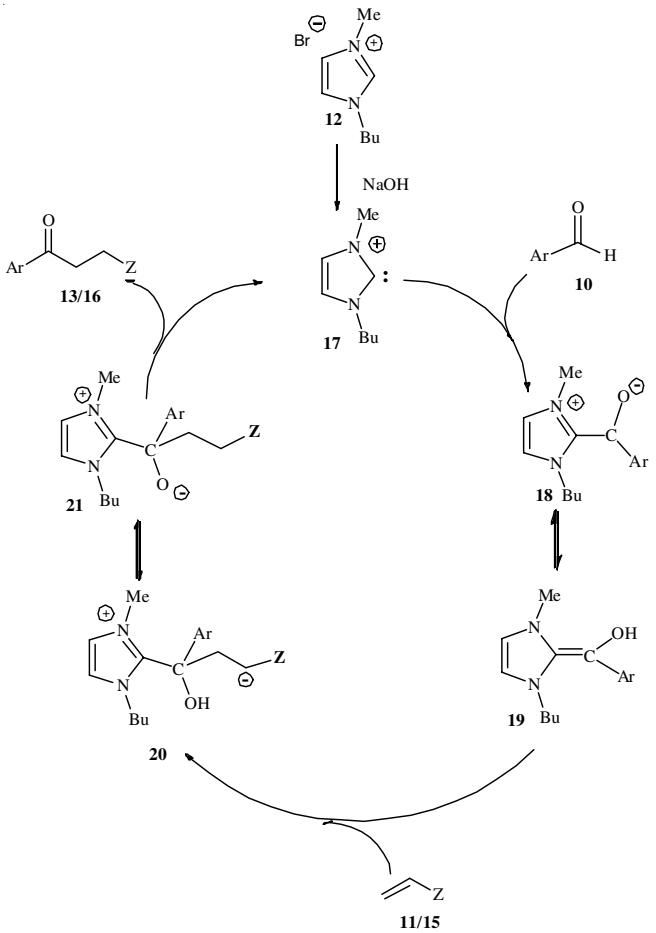
TABLE-2
STETTER REACTION OF AROMATIC ALDEHYDES **10a-d** WITH ACRYLONITRILE (**11**)/ETHYL ACRYLATE (**15**) IN [Bmim]Br (**12**) (100 mol%) IN THE PRESENCE OF NaOH (20 mol%) AT 80 °C



10 **11/15** **13/16** **14**

Entry	Ar	Z	Yield (%)	Yield (%)
1	4-ClC_6H_4 (**10b**)	CN (**11**)	76 (**13b**)	14 (**14b**)
2	4-MeC_6H_4 (**10c**)	CN (**11**)	60 (**13c**)	26 (**14c**)
3	4-C_5H_4N (**10d**)	CN (**11**)	74 (**13d**)	7 (**14d**)
4	C_6H_5 (**10a**)	CO_2Et (**15**)	61 (**16a**)	27 (**14a**)
5	4-ClC_6H_4 (**10b**)	CO_2Et (**15**)	64 (**16b**)	25 (**14b**)
6	4-MeC_6H_4 (**10c**)	CO_2Et (**15**)	51 (**16c**)	30 (**14c**)
7	4-C_5H_4N (**10d**)	CO_2Et (**15**)	63 (**16d**)	10 (**14d**)

Catalytic activity of [Bmim]Br (**12**) results from deprotonation of the 2H proton of imidazolium cation to give NHC **17**. Nucleophilic attrack on aromatic aldehyde **10** produces the adduct intermediate **18**, which proton transfer leads to Breslow intermediate **19**. Subsequent 1,4-addition to the Michael acceptor **11/15** generates 1,4-adduct intermediate **20**. Tranformation to intermediate **21** by proton transfer and liberation of 1,4-addition products **13/16** regenerates the NHC catalyst **17** (**Scheme-V**).



Scheme-V: Catalytic cycle for [Bmim]Br catalyzed Stetter reaction

Conclusion

Stetter reaction between aromatic aldehydes and acrylonitrile/ethyl acrylate in the presence of NaOH 20 mol% in [Bmim]Br 100 mol% proceeded well, with *N*-heterocyclic carbene (NHC) derived from [Bmim]Br as catalyst. Benzoin condensation also took place besides good yields of corresponding 1,4-addition products, giving corresponding aroins as side products. Ethyl acrylate was found to be less reactive than acrylonitrile towards the Stetter reaction.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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